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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/786,502	05/18/2001	Michel Sadelain	MSK.P-040	1539

21121 7590 02/11/2005

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EXAMINER	
HOLLERAN, ANNE L	
ART UNIT	**PAPER NUMBER**
1642	

DATE MAILED: 02/11/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/786,502	SADELAIN ET AL.	
	Examiner	Art Unit	
	Anne Holleran	1642	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *25 June 2004*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-13 and 16-32* is/are pending in the application.

4a) Of the above claim(s) *7-11 and 21-24* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-6,12,13,16-20 and 25-32* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

1. The sequence listing filed June 21, 2004 is acknowledged. The amendment filed March 30, 2004 is acknowledged. Claims 14 and 15 were canceled.

2. Claims 1-13 and 16-32 are pending.

Claims 7-11, and 21-24,drawn to non-elected inventions, are withdrawn from consideration.

Claims 1-6, 12, 13, 16-20 and 25-32 are examined on the merits.

3. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Claim Rejections Withdrawn:

4. The objection to the specification for not complying with the sequence rules is withdrawn in view of the submission on June 21, 2004.

5. The rejection of claims 4, 19, 27 and 31 under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention is withdrawn in view of the amendment.

6. The rejection of claims 1-3, 6, 12, 13, 17, 18, 25, 26, 29 and 30 under 35 U.S.C. 103(a) as being unpatentable over Eshhar et al (US 2002/0137697; published 09/2002; filed 10/1995) in view of Murphy et al ("Murphy I", U.S. Patent 6,383,759; issued 05/2002; filed 05/1998), in view of Murphy et al ("Murphy II", U.S. Patent 5,788.963; issued 08/1998; filed 07/1995) and further in view of Darcy et al (Darcy, P.K. et al., Eur. J. Immunol. 28: 1663-1672, 1998; cited in the IDS) is withdrawn upon further consideration. However, see New Grounds of Rejection below.

7. The rejection of claims 1, 5, 13, 28 and 32 under 35 U.S.C. 103(a) as being unpatentable over either Eshhar et al (US 2002/0137697; published 09/2002; filed 10/1995) or Capon et al (US 5,359,046; issued 10/1994; filed 12/1992) in view of Murphy et al ("Murphy I", U.S. Patent 6,383,759; issued 05/2002; filed 05/1998), in view of Murphy et al ("Murphy II", U.S. Patent 5,788.963; issued 08/1998; filed 07/1995) and further in view of Alderson et al (Alderson et al, Eur. J. Immunol, 24(9): 2219-2227, 1994; abstract only) is withdrawn upon further consideration. However, see New Grounds of Rejection below.

8. The rejection of claims 1, 5, 13, 20, 28 and 32 under 35 U.S.C. 103(a) as being unpatentable over either Eshhar et al (US 2002/0137697; published 09/2002; filed 10/1995) Capon et al (US 5,359,046; issued 10/1994; filed 12/1992) in view of Murphy et al ("Murphy I", U.S. Patent 6,383,759; issued 05/2002; filed 05/1998), in view of Murphy et al ("Murphy II", U.S. Patent 5,788.963; issued 08/1998; filed 07/1995), in view of Darcy et al (Darcy, P.K. et al., Eur. J. Immunol. 28: 1663-1672, 1998; cited in the IDS), and further in view of Alderson et al

(Alderson et al, Eur. J. Immunol, 24(9): 2219-2227, 1994; abstract only) is withdrawn upon further consideration. However, see New Grounds of Rejection below.

9. The rejection of claims 1-3, 6, 12, 17, 18, 29 and 30 under 35 U.S.C. 103(a) as being unpatentable over Capon et al (US 5,359,046; issued 10/1994; filed 12/1992) in view of Murphy et al ("Murphy I", U.S. Patent 6,383,759; issued 05/2002; filed 05/1998), in view of Murphy et al ("Murphy II", U.S. Patent 5;788.963; issued 08/1998; filed 07/1995) and further in view of Darcy et al (Darcy, P.K. et al., Eur. J. Immunol. 28: 1663-1672, 1998; cited in the IDS) is withdrawn upon further consideration. However, see New Grounds of Rejection below.

10. The rejection of claims 14 and 15 under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement is withdrawn in view of the cancellation of the claims.

11. The objection to claims 14 and 15 for reciting an abbreviation without first setting forth the entire name of the term is withdrawn in view of the cancellation of the claims.

Claim Rejections Maintained:

12. The rejection of claims 1-3, 12, 13, 25, 26, 29 and 30 under 35 U.S.C. 103(a) as being unpatentable over Eshhar et al (US 2002/0137697; published 09/2002; filed 10/1995) in view of Murphy et al ("Murphy I", U.S. Patent 6,383,759; issued 05/2002; filed 05/1998) and further in

view of Murphy et al ("Murphy II", U.S. Patent 5,788,963; issued 08/1998; filed 07/1995) is maintained for the reasons of record.

Applicant argues that "the mere fact that teachings found in the prior art could be combined as proposed by the examiner does not make combination obvious absent some teaching, suggestion or incentive to support the combination (Canella v. Starlight Archery and ProLine Co., 804 F.2d 135, 140,231 USPQ 644, 647 (Fed. Cir. 1986) (citing ACS Hosp. Syss; Inc. v. Montefiore Hosp., 732 F. 2d 1572, 1577, 221 USPQ 929, 933 (Fed. Cir. 1984))." In response, it is pointed out that in the original rejection the examiner pointed to teachings in Murphy II that provide a suggestion to combine the teachings of Eshhar with teachings of a PSMA scFv of Murphy II. PSMA is taught to be a useful target for immunological methods of treatment (see col. 3, lines 41-47). Additionally, it is pointed out that Eshhar contains the teachings that the scFv chimeric T cell receptor constructs are made in such a way that any scFv may be substituted for the exemplified scFv (para 82). Furthermore Eshhar contains the general teaching that making chimeric T cell receptors allows one to combine the advantages of the antibody's specificity with the homing, tissue penetration cytokine production and target cell destruction of T lymphocytes and the extend the spectrum of anti-tumor specificity of T cells (para 14). Therefore, because PSMA is a known cancer antigen and because Eshhar clearly taught that any scFv may be used in the chimeric T cell receptor constructs, it appears that the prior art does contain suggestions to combine the teachings of PSMA scFv with the general teachings of chimeric T cell receptors.

Applicant also argues that the rejection is improper because it falls into the class of an "obvious to try" rjection, which is not the standard under 103. Applicant asserts that because

Eshhar fails to exemplify a construct that is the same as that claimed, one of ordinary skill in the art does not have a reasonable expectation of success to try a variation of Eshhar. This argument is not persuasive because Eshhar demonstrates 9 different constructs, which encompass 6 different cytoplasmic domains and 9 different antibodies (scFv portions). In each case, Eshhar demonstrates expression of the fusion protein and in 6 of the constructs Eshhar demonstrates that cells transduced with the chimeric receptors were able to lyse target cells bearing the appropriate antigen (in the other 3 constructs, Eshhar does not appear to have measured lytic activity). Applicant specifically mentions that Eshhar fails to demonstrate that transduced cells undergo proliferation or respond when restimulation occurs. This argument is not persuasive on the point of whether Eshhar is enabling for making a chimeric T cell receptor containing a CD28 cytoplasmic domain (which is a domain not specifically exemplified by Eshhar, but is contemplated), because there are no limitations in the present claims requiring such functionality. Therefore, applicant is arguing limitations not found in the claims. As to the specific portion of CD28 cytoplasmic domain that applicant asserts is not taught by Eshhar, or any of the other cited references, applicants' attention is drawn to the fact that claims 4, 19, 27 and 31 are not longer included in this rejection.

Below is a reiteration of the rejection:

Eshhar teaches chimeric receptors that comprise an scFv that binds a tumor antigen connected to a cytoplasmic domain such as that of a ζ-chain of CD3, or a cytoplasmic domain of CD28 (see page 3, para. 24; para. 19; page 2, para. 17 ; page 11, para. 99). Between the scFv and the cytoplasmic domain is a transmembrane domain, which is interpreted to be a linker (page 1, para 7). Thus, Eshhar teaches constructs that have an scFv that binds a tumor antigen linked

to a cytoplasmic domain via a linker. Eshhar teaches peripheral blood lymphocytes transduced with vectors encoding chimeric receptors (para 119-126).

Eshhar fails to teach a chimeric receptor having an scFv that binds PSMA. However, antibodies to PSMA are known in the art and hybridomas expressing PSMA antibodies are readily available as taught by Murphy I (col. 6). Furthermore, the suggestion to make chimeric receptors that target PSMA is also found in the art; Murphy II teaches that PSMA is a useful target for immunological methods of treatment (see col. 3, lines 41-47). Thus, it would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to have modified the chimeric receptors of Eshhar to comprise an scFv that binds PSMA. One would have been motivated to make such a modification because PSMA has been taught to be a cancer antigen and a target for immune system therapies.

13. The rejection of claims 1-3, 12, 29 and 30 under 35 U.S.C. 103(a) as being unpatentable over Capon et al (US 5,359,046; issued 10/1994; filed 12/1992) in view of Murphy et al ("Murphy I", U.S. Patent 6,383,759; issued 05/2002; filed 05/1998) and further in view of Murphy et al ("Murphy II", U.S. Patent 5,788.963; issued 08/1998; filed 07/1995) is maintained for the reasons of record.

Applicants' arguments have been carefully considered, but fail to persuade. Applicant argues that Capon fails to teach a structure comprising an scFv, because Capon's antibodies include substantial amounts of the constant region of the heavy chain. This argument is not persuasive because at column 8, lines 54-62, Capon teaches that to generate a functional antigen binding site one may construct a "single-chain antibody" (Sab) by fusing together the variable

domains of the heavy and light chains using a short peptide linker, thereby reconstituting an antigen binding site on a single molecule. Capon's constructs also contain CH2 and CH3 regions of the constant region of a heavy chain, but these regions are interpreted by the examiner to be the equivalent of a linker between the scFv portion of the fusion protein and transmembrane and cytoplasmic domains of the T-cell receptor portion of the fusion protein. The claims in the instant application contain no limitations on the chemical nature of the linker. Therefore, the examiner fails to understand why a linker may not take the form of CH2 and CH3 regions of a heavy chain constant domain.

14. The rejection of claims 13 and 16 under 35 U.S.C. 103(a) as being unpatentable over either Eshhar et al (US 2002/0137697; published 09/2002; filed 10/1995) or Capon et al (US 5,359,046; issued 10/1994; filed 12/1992) in view of Murphy et al ("Murphy I", U.S. Patent 6,383,759; issued 05/2002; filed 05/1998), in view of Murphy et al ("Murphy II", U.S. Patent 5,788.963; issued 08/1998; filed 07/1995), and further in view of Gallardo (Gallardo, H.F. et al, Blood, 90: 952-957, 1997; cited in the IDS) is maintained for the reasons of record.

Applicants fail to present specific arguments for why this rejection should be withdrawn.

The rejection is reiterated below:

Claims 13 and 16 are drawn to expression vectors encoding chimeric fusion receptors where the expression vector is packaged in gibbon ape leukemia virus (GaLV) enveloped pseudotyped virions. The combination of Eshar or Capon with Murphy I and Murphy II teach expression vectors encoding a chimeric fusion receptor that is packaged into retrovirus particles for transfection. The combination fails to teach the specific virus that is gibbon ape leukemial

virus. However, Gallardo teaches the use of such viruses for transfection into primary T lymphocytes, and that virus particles psuedotyped with he GaLV envelope are far more infectious on a particulate basis than the vesicular stomatisitis virus. Therefore, it would have been obvious to one of ordinary skill in the art to have modified the teachings of either Eshhar or Capon by using GaLV envelope pseudotype virions as taught by Gallardo. One would have been motivated to use the teachings of Gallardo because of the high efficiency of gene transfer achievable with such constructs.

New Grounds of Rejection:

15. Claims 4, 19, 27 and 31 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter that was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. The basis for this rejection is that the claims and the specification are incomplete because no PCR template is described in either the claims or the specification.

Claim 4 is drawn to a fusion receptor where the cytoplasmic domain of the fusion receptor is encoded by a portion of CD28 cDNA which is obtained when CD28 cDNA is amplified using primers of SEQ ID Nos: 7 and 8. Applicants indicate that support for this amendment is found in example 6. However, while the specification does describe work that was done with SEQ ID Nos: 7 and 8 to define a nucleotide segment to be used in the making of a fusion receptor, the specification fails to describe the PCR parameters that were used or the template that was used. The specification refers to something called "pbsCD28", but fails to

give a reference or a description of this. Therefore, the structure of the polynucleotide that was inserted into the fusion construct cannot be determined from the specification and does not appear to be described. Also, confusing is the fact that the specification appears to indicate that a polynucleotide structure encompassing encoding amino acids 336-663 of CD28 was used in making the fusion construct of example 6. This is confusing because according to the sequence provided by Aruffo and Seed (Figure 2, Proc. Natl. Acad. Sci. USA, 84: 8573-8577, 1987) human CD28 only contains 202 amino acids. Alternatively, if applicant intended to write nucleotides 336-663 of CD28, this does not appear to be the case because SEQ ID NO: 7 and SEQ ID NO: 8 would be useful, if human CD28 cDNA were the template, to amplify a region from nucleotides 438-762.

Vas-Cath Inc. v. Mahurkar, 19 USPQ2d 111, makes clear that "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession *of the invention*. The invention is for purposes of the 'written description' inquiry, "*whatever is now claimed*" (see page 1117). The specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is now claimed." (See Vas-Cath at page 1116.)

The skilled artisan cannot envision the detailed chemical structure of the encompassed fusion protein that comprises a cytoplasmic domin encoded by a portion of CD28 cDNA, which is obtained when CD28 cDNA is amplified using primers of SEQ ID Nos: 7 and 8, regardless of the complexity or simplicity of the method of manufacturing or testing the claimed process. Without specifying the template and the PCR conditions employed the claim broadly reads on fusion constructs that contain CD28 cDNA portions from any species, or that contain allelic

variants or mutants of CD28 that have not been described. Adequate written description requires more than a mere statement that it is part of the invention and reference to a potential method for making or testing it. One cannot describe what one has not conceived. See Fiddes v. Baird, 30 USPQ2d 1481, 1483. In Fiddes v. Baird, claims directed to mammalian FGF's were found unpatentable due to lack of written description for the broad class. Applicant is reminded that Vas-Cath makes clear that the written description provision of 35 U.S.C. 112, is severable from its enablement provision. (See page 1115).

16. Claims 1-3, 6, 12, 13, 17, 18, 25, 26, 29 and 30 are rejected under 35 U.S.C. 103(a) as being unpatentable over Eshhar et al (US 2002/0137697; published 09/2002; filed 10/1995) in view of Murphy et al ("Murphy I", U.S. Patent 6,383,759; issued 05/2002; filed 05/1998), in view of Murphy et al ("Murphy II", U.S. Patent 5,788.963; issued 08/1998; filed 07/1995) and further in view of Moritz et al (Moritz, D. et al., Gene Therapy 2: 539-545, 1995; cited in the IDS).

Claims 1-3, 6, 12, 13, 17, 18, 25, 26, 29 and 30 may be interpreted to read on fusion receptors having a connector between the scFv portion of the fusion protein and the cytoplasmic domain of the T-cell receptor, where the connector is a CD8 hinge, and expression vectors comprising nucleic acids encoding said fusion receptors. While Eshhar teaches that fusion receptors comprising cytoplasmic and transmembrane domains of T-cell receptors such as CD3 will also include short extracellular domains which can serve for the attachment of the scFv (interpreted to be a "connector" between the T-cell receptor cytoplasmic domain and the scFv portion; see para 57), the combination of Eshhar, Murphy I and Murphy II fails to teach fusion

receptors comprising a connector that is a CD8 hinge. However, the requirement of a connector region (or "spacer" region) between the scFv portion of the fusion protein and the T-cell receptor cytoplasmic domain portion of the fusion protein is known in the art as demonstrated by the teachings of Moritz. Moritz teaches that a spacer region is required for efficient ligand binding and signaling activity. Moritz teaches two examples of spacer regions. One is a CD8 hinge region, and the other is D3/D4 membrane –proximal Ig-like domains of the murine CD4 molecule. Moritz teaches fusion proteins comprising an anti-ErbB2 scFv and CD3 ζ transmembrane and cytoplasmic domain. Fusion proteins that lack a connector (spacer region) between the scFv and the transmembrane and cytoplasmic domain portion do not efficiently bind antigen. Thus, it would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to have used a linker that is a CD8 hinge, because the need for a spacer region was known at the time of the invention and because it was known that a CD8 hinge is a useful spacer region. One would have had a reasonable expectation of success in making a fusion protein having a CD8 hinge that bound antigen because both Eshhar and Moritz teach fusion receptors comprising a polypeptide region that served as a spacer region connected to a CD3 ζ chain, which functioned as the cytoplasmic domain portion of the fusion protein. One would have been motivated to use the CD8 hinge of Moritz because the function of the CD8 hinge is that of a spacer region that enables the scFv portion of the fusion protein to bind antigen when the fusion protein is expressed in T cells. It appears that the prior art recognized the need for a spacer region and the particular nature of the spacer region is not important. Applicant has failed to show that there would be an unexpected benefit to using the CD8 hinge over any other type of spacer region.

17. Claims 1-3, 6, 12, 17, 18, 29 and 30 are rejected under 35 U.S.C. 103(a) as being unpatentable over Capon et al (US 5,359,046; issued 10/1994; filed 12/1992) in view of Murphy et al ("Murphy I", U.S. Patent 6,383,759; issued 05/2002; filed 05/1998), in view of Murphy et al ("Murphy II", U.S. Patent 5,788.963; issued 08/1998; filed 07/1995) and further in view of Moritz (Moritz, D. et al., Gene Therapy 2: 539-545, 1995; cited in the IDS).

While Capon teaches that fusion receptors comprising cytoplasmic and transmembrane domains of T-cell receptors such as CD3 will be attached to the scFv portion of the fusion receptor via CH2 and CH3 domains (interpreted to be a "connector" between the T-cell receptor cytoplasmic domain and the scFv portion; see col. 9, lines 5-23), the combination of Capon, Murphy I and Murphy II fails to teach fusion receptors comprising a linker that is a CD8 hinge. However, the requirement of a connector region (or "spacer" region) between the scFv portion of the fusion protein and the T-cell receptor cytoplasmic domain portion of the fusion protein is known in the art as demonstrated by the teachings of Moritz. Moritz teaches that a spacer region is required for efficient ligand binding and signaling activity. Moritz teaches two examples of spacer regions. One is a CD8 hinge region, and the other is D3/D4 membrane –proximal Ig-like domains of the murine CD4 molecule. Moritz teaches fusion proteins comprising an anti-ErbB2 scFv and CD3 ζ transmembrane and cytoplasmic domain. Fusion proteins that lack a connector (spacer region) between the scFv and the transmembrane and cytoplasmic domain portion do not efficiently bind antigen. Thus, it would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to have used a linker that is a CD8 hinge, because the need for a spacer region was known at the time of the invention and because it was known that a CD8 hinge is a useful spacer region. One would have had a reasonable expectation of success in

making a fusion protein having a CD8 hinge that bound antigen because both Capon and Moritz teach fusion receptors comprising a polypeptide region that served as a spacer region connected to a CD3 ζ chain, which functioned as the cytoplasmic domain portion of the fusion protein. One would have been motivated to use the CD8 hinge of Moritz because the function of the CD8 hinge is that of a spacer region that enables the scFv portion of the fusion protein to bind antigen when the fusion protein is expressed in T cells. It appears that the prior art recognized the need for a spacer region and the particular nature of the spacer region is not important. Applicant has failed to show that there would be an unexpected benefit to using the CD8 hinge over any other type of spacer region.

18. Claims 1, 5, 13, 28 and 32 are rejected under 35 U.S.C. 103(a) as being unpatentable over either Eshhar et al (US 2002/0137697; published 09/2002; filed 10/1995) or Capon et al (US 5,359,046; issued 10/1994; filed 12/1992) in view of Murphy et al ("Murphy I", U.S. Patent 6,383,759; issued 05/2002; filed 05/1998), in view of Murphy et al ("Murphy II", U.S. Patent 5,788,963; issued 08/1998; filed 07/1995) and further in view of Alvarez-Vallina (Alvarez-Vallina, L. et al., Eur. J. Immunol., 26: 2304-2309, 1996 ; cited in the IDS) and Hurtado (Hurtado, J.C. et al., Journal of Immunology, 158: 2600-2609, 1997).

Neither Eshhar nor Capon teaches cytoplasmic domains that are the 4-1BB cytoplasmic domain. However, both Eshhar and Capon teach generally that cytoplasmic domains may be the cytoplasmic domains of T-cell receptors. Alvarez-Vallina teaches that CD28 is a co-stimulatory signal that optimally activates T-cells. Alvarez-Vallina also teaches fusion protein comprising an scFv fused to a portion of the CD28 protein that includes part of the extracellular domain, the

transmembrane domain and the entire cytoplasmic domain. Hurtado teaches that 4-1BB is also a T cell receptor that functions similarly to the CD28 receptor. Thus, it would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to have made a fusion receptor as claimed, which fusion receptor comprises a cytoplasmic domain of a 4-1BB T cell receptor, by modifying the teachings of either Eshhar or Capon to use a 4-1BB receptor instead of the exemplified receptors of either reference. One would have been motivated to use the 4-1BB receptor because either of Eshhar or Capon teaches generally that cytoplasmic domains of T cell receptors are useful in making chimeric T cell receptors and because the combination of Alvarez-Vallina and Hurtado demonstrates the importance of co-stimulatory T-cell receptors in the immune function of T-cells.

19. Claims 1, 5, 13, 20, 28 and 32 are rejected under 35 U.S.C. 103(a) as being unpatentable over either Eshhar et al (US 2002/0137697; published 09/2002; filed 10/1995) or Capon et al (US 5,359,046; issued 10/1994; filed 12/1992) in view of Murphy et al ("Murphy I", U.S. Patent 6,383,759; issued 05/2002; filed 05/1998), in view of Murphy et al ("Murphy II", U.S. Patent 5,788,963; issued 08/1998; filed 07/1995), in view of Alvarez-Vallina (Alvarez-Vallina, L. et al., Eur. J. Immunol., 26: 2304-2309, 1996 ; cited in the IDS) and Hurtado (Hurtado, J.C. et al., Journal of Immunology, 158: 2600-2609, 1997) and further in view of Moritz (Moritz, D. et al., Gene Therapy 2: 539-545, 1995; cited in the IDS).

While either of Eshhar or Capon teaches that fusion receptors comprising cytoplasmic and transmembrane domains of T-cell receptors such as CD3 will be attached to the scFv portion of the fusion receptor via polypeptide segments that function as connectors between the scFv

portion of the fusion receptor and the T-cell receptor cytoplasmic domain, the combination of Eshhar or Capon, Murphy I and Murphy II, Alvarez-Vallina and Hurtado fails to teach fusion receptors comprising a linker that is a CD8 hinge. However, the requirement of a connector region (or "spacer" region) between the scFv portion of the fusion protein and the T-cell receptor cytoplasmic domain portion of the fusion protein is known in the art as demonstrated by the teachings of Moritz. Moritz teaches that a spacer region is required for efficient ligand binding and signaling activity. Moritz teaches two examples of spacer regions. One is a CD8 hinge region, and the other is D3/D4 membrane –proximal Ig-like domains of the murine CD4 molecule. Moritz teaches fusion proteins comprising an anti-ErbB2 scFv and CD3 ζ transmembrane and cytoplasmic domain. Fusion proteins that lack a connector (spacer region) between the scFv and the transmembrane and cytoplasmic domain portion do not efficiently bind antigen. Thus, it would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to have used a linker that is a CD8 hinge, because the need for a spacer region was known at the time of the invention and because it was known that a CD8 hinge is a useful spacer region. One would have had a reasonable expectation of success in making a fusion protein having a CD8 hinge that bound antigen because Eshhar, Capon and Moritz teach fusion receptors comprising a polypeptide region that served as a spacer region connected to a CD3 ζ chain, which functioned as the cytoplasmic domain portion of the fusion protein. One would have been motivated to use the CD8 hinge of Moritz because the function of the CD8 hinge is that of a spacer region that enables the scFv portion of the fusion protein to bind antigen when the fusion protein is expressed in T cells. It appears that the prior art recognized the need for a spacer region and the particular nature of the spacer region is not important. Applicant has

failed to show that there would be an unexpected benefit to using the CD8 hinge over any other type of spacer region.

20. Claims 1, 3, 12, 13, 26, and 30 are rejected under 35 U.S.C. 103(a) as being unpatentable over Eshhar et al (US 2002/0137697; published 09/2002; filed 10/1995) in view of Murphy et al ("Murphy I", U.S. Patent 6,383,759; issued 05/2002; filed 05/1998), in view of Murphy et al ("Murphy II", U.S. Patent 5,788,963; issued 08/1998; filed 07/1995), and further in view of Alvarez-Vallina (Alvarez-Vallina, L. et al, Eur. J. Immunol. 26: 2304-2309, 1996; cited in the IDS).

Claims 1, 3, 12, 13, 26, and 30 are interpreted as drawn to fusion receptors of claim 1, wherein the cytoplasmic domain is a CD28 cytoplasmic domain. In previous arguments, applicants have argued that Eshhar's teaching of a fusion protein comprising a CD28 T-cell receptor cytoplasmic domain is prophetic and not enabling, because one of ordinary skill in the art would not have a reasonable expectation of success in making such a fusion protein. This argument is not persuasive because Alvarez-Vallina successfully made fusion receptors that comprise the CD28 cytoplasmic domain. Therefore, in view of the teachings of Alvarez-Vallina, it would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to have combined the teachings of Eshhar with that of Murphy I and Murphy II to make a fusion protein comprising an anti-PSMA scFv and a CD28 cytoplasmic domain because both Eshhar and Alvarez-Vallina teach fusion proteins comprising CD28 cytoplasmic domains, and Alvarez-Vallina exemplifies a fusion receptor comprising a CD28 cytoplasmic domain. With regard to making fusion receptors that comprise an anti-PSMA scFv, Eshhar contains the

general teaching that making chimeric T cell receptors allows one to combine the advantages of the antibody's specificity with the homing, tissue penetration cytokine production and target cell destruction of T lymphocytes and the extend the spectrum of anti-tumor specificity of T cells (para 14). Therefore, because PSMA is a known cancer antigen and because Eshhar clearly taught that any scFv may be used in the chimeric T cell receptor constructs, it appears that the prior art contains suggestions to combine the teachings of PSMA scFv with the general teachings of chimeric T cell receptors.

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970);and, *In re Thorington,* 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

21. Claims 3 and 26 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1, 2, 8, and 9 of copending Application No. 08/940,544 in view of Murphy I and Murphy II.

This is a provisional obviousness-type double patenting rejection.

Claims 3 and 26 are drawn to polypeptides comprising fusion proteins comprising an anti-PSMA scFv linked to a CD28 cytoplasmic domain, where the linkage may be via an

optional linker; the claims are also drawn polynucleotides encoding such polypeptides. The subject matter of claims 3 and 26 is encompassed by the subject matter of claims 1, 2, 8 and 9 of copending application 08/940,544, which are drawn to nucleic acids encoding fusion proteins comprising a single chain antibody, a signaling domain of human CD28 and a transmembrane domain, where the transmembrane domain is disposed between the single-chain antibody and the signaling domain of human CD28. The specification of copending application 08/940,544 teaches that preferred embodiments of the single-chain antibody may be an anti-PSMA single chain antibody or an anti-GD2 single chain antibody (see page 7, lines 7-10). In view of the teachings of Murphy I and Murphy II, which place the structures of PSMA antibodies and single chain antibodies into the public domain, it would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to make the fusion proteins and nucleic acids the comprise a an anti-PSMA scFV linked to a CD28 cytoplasmic domain. Therefore, the species of claims 3 and 26 of the instant application appear to be obvious species of the genus of fusion proteins and nucleic acids of claims 1, 2, 8 and 9 of copending application 08/940,544.

Conclusion

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the Office should be directed to Anne Holleran, Ph.D. whose telephone number is (571) 272-0833. Examiner Holleran can normally be reached Monday through Friday, 9:30 am to 3:30 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Jeffrey Siew, can be reached at (571) 272-0787.

Any inquiry of a general nature or relating to the status of this application should be directed to the Group receptionist at telephone number (703) 571-1600.

Anne L. Holleran
Patent Examiner
February 6, 2005

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02/07/2005